Into each of three beagle dogs weighing 9 to 12 kg which had fasted a day and night, tetragastrin (10 μg/kg body weight) was intramuscularly injected. Ninety minutes after the injection, one of the pharmaceutical preparation containing 10 mg of prednisolone and 20 mg of theophylline as the gastric emptying indicator obtained in the above was orally administered to each beagle dog together with 50 mℓ of purified water. After administration, the blood was collected at predetermined times and the concentration (μg/mℓ) of prednisolone and theophilline in the plasma was determined.

The change of the concentration of prednisolone in the plasma is shown in Fig. 6 using the mean of the determined three concentrations. The concentration of the medicament in the plasma quickly increased from about 3 hours after the gastric emptying and reached a maximum about 5 hours after the gastric emptying. These results suggest that in the pharmaceutical preparation of the present invention, a medicament is released and then satisfactorily absorbed.

Experimental Example 2

(1) Preparation Method

A white hard gelatin capsule of Size No. 2 (commercially available from CAPSUGEL AG, Japan) was filled with a mixture of 20 mg of theophylline and 100 mg of succinic acid to obtain a core capsule.

The core capsule was spray-coated with a 5 % by weight coating solution of Eudragit E100 (trade name, methyl methacrylate-butyl methacrylate-dimethylaminoethyl methacrylate copolymer, commercially available from Röhm Pharma, Germany) dissolved in ethanol, in a coating amount of 20, 30, 40, 50, 60, 70, 80, 90 or 100 mg per capsule as Eudragit E100 by means of HICOATER (trade name, made by Freund Industrial Co., Ltd., Japan) to obtain nine kinds of capsules coated with a low pH-soluble polymer film, which differed from each other in the amount of the low pH-soluble polymer film.

(2) Dissolution Test

With respect to each of nine kinds of the preparations obtained in the above (1), the dissolution test was carried out with the JP 2nd-Fluid under the same conditions as in Experimental Example 1(1).

The results of the dissolution test are shown in Fig. 7. Fig. 8 shows the relationship between the lag-time and the coating amount of Eudragit E100, which was based on the results of the dissolution test. It is understood that according to the pharmaceutical preparation of the present invention, a lag-time can be easily and widely controlled by the amount of the low pH-soluble polymer film. In addition, it is understood that in each preparation, it takes about 1 hour after each start of dissolution to dissolve 80 % of the medicament and therefore the increase of the amount of the low pH-soluble polymer film does not influence the dissolution rate of the medicament.

Experimental Example 3

(1) Preparation Method

Each white hard gelatin capsule of Size No. 2 (commercially available from CAPSUGEL AG, Japan) was filled with a mixture of 20 mg of theophylline and 100 mg of maleic acid, tartaric acid, fumaric acid or citric acid to obtain four kinds of core capsules. To each of the core capsules, a sealing means (1.5 % by weight, based on the weight of the used empty hard capsule) was provided around the joint of the body and the cap of the core capsule by applying a 10 % by weight solution of ethylcellulose in ethanol on the joint using a Pasteur pipet and by drying using a dryer to seal the joint.

The obtained core capsule with a sealing means was subjected to the same procedure as in the following Example 1(2). Thus there were obtained four kinds of capsules coated with a low pH-soluble polymer film, which differed from each other in the kind of the acidic substance.

(2) Dissolution Test

With respect to each of four kinds of the preparations obtained in the above (1), the dissolution test was carried out with the JP 2nd-Fluid under the same conditions as in Experimental Example 1(1).

The results of the dissolution test are shown in Fig. 9. It is understood that according to the pharmaceutical preparation of the present invention, a lag-time can be controlled by changing the kind of the acidic substance. In addition, it is understood that in each preparation, it takes about 1 hour after the start of release to release 80 % of the medicament, and therefore the kind of the acidic substance does not influenc the dissolution rate of the medicament.

Experimental Example 4

(1) Preparation Method

A white hard gelatin capsule of Size No. 2 (commercially available from CAPSUGEL AG, Japan) was filled with a mixture of 20 mg of theophylline and 0, 10, 20, 50 or 100 mg of succinic acid to obtain five kinds of core capsules.

The core capsules were subjected to the same procedures as in the following Example 1(2) and 1(3) to obtain five kinds of pharmaceutical preparations of the present invention, which differed from each other in the amount of the acidic substance.

(2) Dissolution Test

With respect to each of five kinds of the pharmaceutical preparations obtained in the above (1), the dissolution test was carried out with the JP 2nd-Fluid under the same conditions as in Experimental Example 1(1).

The results of the dissolution test are shown in Fig. 10. It is understood that the lag-time and the dissolution rate of a medicament are hardly influenced by the amount of succinic acid when the amount of succinic acid per a capsule becomes at least about 20 mg.

Experimental Example 5

Dissolution Test

With respect to the pharmaceutical preparations (n=6) wherein a sealing means is provided, obtained in the following Example 2, the dissolution test was carried out with the JP 2nd-Fluid under the same condition as in Experimental Example 1(1).

The results of the dissolution test are shown in Fig. 11. It is understood that the pharmaceutical preparation of the present invention wherein a sealing means is provided around the joint of the body and the cap of the capsule is excellent because of having quite little deviation of the dissolution pattern.

Example 1

(1) A white hard gelatin capsule of Size No. 2 (63 mg) (commercially available from CAPSUGEL AG, Japan) was filled with a mixture of 10 mg of prednisolone and 100 mg of succinic acid to obtain a core capsule.

(2) The core capsule was spray-coated with a 5 % by weight solution of Eudragit E100 (trade name, methyl methacrylate-butyl methacrylate-dimethylaminoethyl methacrylate copolymer, commercially available from Röhm Pharma, Germany) dissolved in ethanol, in a coating amount of 30 mg per capsule (48 % by weight, based on the weight of the used empty hard capsule) as Eudragit E100 by means of HICOATER (trade name, made by Freund Industrial Co., Ltd., Tokyo, Japan, hereinafter the same) to obtain a capsule coated with a low pH-soluble polymer film.

(3) Thus obtained coated capsule was further spray-coated with a coating solution, which was prepared by dissolving HPMC-AS (trade name, hydroxypropylmethylcellulose acetate succinate, commercially available from Shin-Etsu Chemical Co., Ltd., Japan) in a mixture of ethanol and water (5:3 (w/w)) to obtain a 5 % by weight HPMC-AS solution and adding thereto talc in an amount of 2.5 % by weight, based on the total weight of the 5 % HPMC-AS solution, in a coating amount of 100 mg per capsule (159 % by weight, based on the weight of the used empty hard capsule) as HPMC-AS by means of HICOATER.

Thus a pharmaceutical preparation of the present invention was obtained in the form of a coated capsule releasable at the lower part of the digestive tract.

Example 2

(1) A white hard gelatin capsule of Size No. 2 (commercially available from CAPSUGEL AG, Japan) was filled with a mixture of 20 mg of theophylline and 100 mg of succinic acid to obtain a core capsule. To the joint of the body and the cap of the core capsule, a sealing means (1.5 % by weight, based on the weight of the used empty hard capsule) was provided by applying a 10 % by weight solution of ethylcellulose in ethanol using a Pasteur pipet and by drying using a dryer to seal the joint.

(2) The obtained core capsule with a sealing means was subjected to the same procedures as in Example 1(2) and 1(3) to obtain a pharmaceutical preparation of the present invention wherein a sealing means is provided around the joint of the hard capsule.

Example 3

(1) A white hard gelatin capsule of Size No. 2 (commercially available from CAPSUGEL AG, Japan) was filled with a mixture of 10 mg of prednisolone and 100 mg of succinic acid to obtain a core capsule. To the joint of the body and the cap, a sealing means (1.5 % by weight, based on the weight of the used empty hard capsule) was provided by applying a 10 % by weight solution of ethylcellulose in ethanol using a Pasteur pipet and by drying using a dryer to seal the joint.

(2) The obtained core capsule with a sealing means was subjected to the same procedure as in Example 1(2) to obtain a capsule coated with a low pH-soluble polymer film.

(3) Thus obtained coated capsule was further spray-coated with a 5 % by weight aqueous solution of TC-5 (trade name, hydroxypropylmethylcellulose, commercially available from Shin-Etsu Chemical Co., Ltd., Japan) in a coating amount of 15 mg per capsule (24 % by weight, based on the weight of the used empty hard capsule) by means of HICOATER to obtain a double-coated capsule wherein the low pH-soluble polymer film is further coated with an intermediate layer.

(4) Thus obtained double-coated capsule was subjected to the same procedure as in Example 1(3) to obtain a pharmaceutical preparation of the present invention wherein a sealing means and an intermediate layer are provided.

Example 4

(1) A white hard gelatin capsule of Size No. 2 (commercially available from CAPSUGEL AG, Japan) was filled with a mixture of 20 mg of theophylline and 100 mg of tartaric acid to obtain a core capsule.

(2) The obtained core capsule was subjected to the same procedures as in Example 1(2) and 1(3) to obtain a pharmaceutical preparation of the present invention.

Example 5

(1) A white hard HPMC capsule of Size No. 2 (commercially available from Japan Elanco CO., LTD., Japan) was filled with a mixture of 20 mg of theophylline and 100 mg of succinic acid to obtain a core capsule.

(2) The obtained core capsule was subjected to the same procedures as in Example 1(2) and 1(3) to obtain a pharmaceutical preparation of the present invention.

Example 6

(1) A white hard gelatin capsule of Size No. 2 (commercially available from CAPSUGEL AG, Japan) was filled with a mixture of 20 mg of theophylline and 100 mg of maleic acid to obtain a core capsule.

(2) The obtained core capsule was subjected to the same procedures as in Example 1(2) and 1(3) to obtain a pharmaceutical preparation of the present invention.

Example 7

(1) A white hard gelatin capsule of Size No. 2 (commercially available from CAPSUGEL AG, Japan) was filled with a mixture of 20 mg of theophylline and 100 mg of citric acid to obtain a core capsule.

(2) The obtained core capsule was subjected to the same procedures as in Example 1(2) and 1(3) to obtain a pharmaceutical preparation of the present invention.

Example 8

(1) A white hard gelatin capsule of Size No. 2 (commercially available from CAPSUGEL AG, Japan) was filled with a mixture of 20 mg of theophylline and 100 mg of fumaric acid to obtain a core capsule.

(2) The obtained core capsule was subjected to the same procedures as in Example 1(2) and 1(3) to obtain a pharmaceutical preparation of the present invention.

Example 9

(1) A white hard gelatin capsule of Size No. 2 (commercially available from CAPSUGEL AG, Japan) was filled with a mixture of 20 mg of theophylline and 100 mg of malic acid to obtain a core capsule.

(2) The obtained core capsule was subjected to the same procedures as in Example 1(2) and 1(3) to obtain a pharmaceutical preparation of the present invention.

Example 10

(1) A white hard gelatin capsule of Size No. 2 (commercially available from CAPSUGEL AG, Japan) was filled with a mixture of 20 mg of theophylline and 100 mg of succinic acid to obtain a core capsule.

(2) The core capsule was spray-coated with a 5 % by weight solution of polyvinylacetal diethylaminoacetate in ethanol in a coating amount of 30 mg per capsule (48 % by weight, based on the weight of the used empty hard capsule) as polyvinylacetal diethylaminoacetate by means of HICOATER to obtain a capsule coated with a low pH-soluble polymer film.

(3) Thus obtained coated capsule was subjected to the same procedure as in Example 1(3) to obtain a pharmaceutical preparation of the present invention.

Example 11

(1) A white hard gelatin capsule of Size No. 2 (commercially available from CAPSUGEL AG, Japan) was filled with a mixture of 10 mg of prednisolone and 100 mg of succinic acid to obtain a core capsule.

(2) The core capsule was subjected to the same procedure as in Example 1(2) to obtain a capsule coated with a low pH-soluble polymer film.

(3) Thus obtained coated capsule was further spray-coated with a coating solution, which was prepared by dissolving hydroxypropylmethylcellulose phthalate in a mixture of ethanol and water (8:2 (w/w)) to obtain a 5 % by weight solution of hydroxypropylmethylcellulose phthalate and adding thereto talc in an amount of 2.5 % by weight, based on the total weight of the 5 % solution, in a coating amount of 80 mg per capsule (127 % by weight, based on the weight of the used empty hard capsule) as hydroxypropylmethylcellulose phthalate by means of HICOATER.

Thus a pharmaceutical preparation of the present invention was obtained in the form of a coated capsule releasable at the lower part of the digestive tract.

Example 12

(1) A white hard gelatin capsule of Size No. 2 (commercially available from CAPSUGEL AG, Japan) was filled with a mixture of 10 mg of prednisolone and 100 mg of succinic acid to obtain a core capsule.

(2) The core capsule was subjected to the same procedure as in Example 1(2) to obtain a capsule coated with a low pH-soluble polymer film.

(3) Thus obtained coated capsule was further spray-coated with a coating solution, which was prepared by dissolving cellulose acetate phthalate in a mixture of ethanol and water (8:2 (w/w)) to obtain a 5 % by weight solution of cellulose acetate phthalate and adding thereto talc in an amount of 5 % by weight, based on the total weight of the 5 % solution, in a coating amount of 100 mg per capsule (159 % by weight, based on the weight of the used empty hard capsule) as cellulose acetate phthalate by means of HICOATER.

Thus a pharmaceutical preparation of the present invention was obtained in the form of a coated capsule releasable at the lower part of the digestive tract.

Example 13

(1) A white hard gelatin capsule of Size No. 2 (commercially available from CAPSUGEL AG, Japan) was filled with a mixture of 10 mg of prednisolone and 100 mg of succinic acid to obtain a core capsule.

(2) The core capsule was subjected to the same procedure as in Example 1(2) to obtain a capsule coated with a low pH-soluble polymer film.

(3) Thus obtained coated capsule was further spray-coated with a coating solution, which was prepared by dissolving Eudragit L100 (trade name, methacrylic acid-methyl methacrylate copolymer, commercially available from Röhm Pharma, Germany) in a mixture of ethanol and water (8:2 (w/w)) to obtain a 5 % by weight solution of Eudragit L100 and adding thereto talc in an amount of 5 % by weight, based on the total weight of the 5 % Eudragit L100 solution, in a coating amount of 80 mg per capsule (127 % by weight, based on the weight of the used empty hard capsule) as Eudragit L100 by means of HICOATER.

Thus a pharmaceutical preparation of the present invention was obtained in the form of a coated capsule releasable at the lower part of the digestive tract.

Example 14

(1) A white hard gelatin capsule of Size No. 2 (commercially available from CAPSUGEL AG, Japan) was filled with a mixture of 10 mg of prednisolone and 100 mg of succinic acid to obtain a core capsule.

(2) The core capsule was subjected to th same procedure as in Example 1(2) to obtain a capsule coated with a low pH-soluble polymer layer.

(3) Thus obtained coated capsule was further spray-coated with a coating solution, which was prepared by dissolving Eudragit S100 (trade name, methacrylic acid-methyl methacrylate copolymer, commercially available from Röhm Pharma, Germany) in a mixture of ethanol and water (8:2 (w/w)) to obtain a 5 % by weight solution of Eudragit S100 and adding thereto talc in an amount of 5 % by weight, based on the total weight of the 5 % Eudragit S100 solution, in a coating amount of 90 mg per capsule (143 % by weight, based on the weight of the used empty hard capsule) as Eudragit S100 by means of HICOATER.

Thus a pharmaceutical preparation of the present invention was obtained in the form of a coated capsule releasable at the lower part of the digestive tract.

Example 15

(1) A white hard gelatin capsule of Size No. 2 (commercially available from CAPSUGEL AG, Japan) was filled with a mixture of 10 mg of prednisolone and 100 mg of succinic acid to obtain a core capsule.

(2) The core capsule was subjected to the same procedure as in Example 1(2) to obtain a capsule coated with a low pH-soluble polymer film.

(3) Thus obtained coated capsule was further spray-coated with a coating solution, which was prepared by dissolving Eudragit L100-55 (trade name, methacrylic acid-ethyl acrylate copolymer, commercially available from Röhm Pharma, Germany) in a mixture of ethanol and water (8:2 (w/w)) to obtain a 5 % by weight solution of Eudragit L100-55 and adding thereto talc in an amount of 5 % by weight, based on the total weight of the 5 % solution of Eudragit L100-55, in a coating amount of 100 mg per capsule (159 % by weight, based on the weight of the used empty hard capsule) as Eudragit L100-55 by means of HICOATER.

Thus a pharmaceutical preparation of the present invention was obtained in the form of a coated capsule releasable at the lower part of the digestive tract.

In addition to the ingredients used in the Examples, other ingredients can be used in the Examples as set forth in the specification to obtain substantially the same results.

Claims

1. A pharmaceutical preparation in the form of a coated capsule which can release contents of a capsule at a lower part of the digestive tract comprising (a) a hard capsule containing at least an acidic substance, (b) a polymer film soluble at low pH which is formed on a surface of said hard capsule, and (c) an enteric coating film which is formed on a surface of said polymer film soluble at low pH.

2. The pharmaceutical preparation of Claim 1 wherein at least one member selected from the group consisting of a medicament, a pharmaceutical preparation and a functional substance is contained in said hard capsule.

3. The pharmaceutical preparation of Claim 1 or 2 wherein a sealing means is provided around a joint of a body and a cap of said hard capsule.

4. The pharmaceutical preparation of Claim 1, 2 or 3 wherein said acidic substance is a solid substance of which aqueous solution has pH value of at most 5.

5. The pharmaceutical preparation of Claim 1, 2, 3 or 4 wherein said acidic substance is at least one member selected from the group consisting of an organic acid and an inorganic acid.

6. The pharmaceutical preparation of Claim 1, 2, 3, 4 or 5 wherein said polymer film soluble at low pH comprises at least one member selected from the group consisting of polyvinyl acetal diethylaminoacetate, methyl methacrylate-butyl methacrylate-dimethylaminoethyl methacrylate copolymer and polyvinyl aminoacetal.

7. The pharmaceutical preparation of Claim 1, 2, 3, 4, 5 or 6 wherein said enteric coating film comprises at least one member selected from the group consisting of hydroxypropylmethylcellulose acetate succinate, hydroxypropylmethylcellulose phthalate, hydroxymethylethylcellulose phthalate, cellulose acetate phthalate, cellulose acetate succinate, cellulose acetate malate, cellulose benzoate phthalate, cellulose propionate phthalate, methylcellulose phthalate, carboxymethylethylcellulose, ethylhydroxyethylcellulose phthalate, shellac, styrene-acrylic acid copolymer, methyl acrylate-acrylic acid copolymer, methyl acrylate-methacrylic acid copolymer, butyl acrylate-styrene-

acrylic acid copolymer, methacrylic acid-methyl methacrylate copolymer, methacrylic acid-ethyl acrylate copolymer, methyl acrylate-methacrylic acid-octyl acrylate copolymer, vinyl acetate-maleic acid anhydride copolymer, styrene-maleic acid anhydride copolymer, styrene-maleic acid monoester copolymer, vinyl methyl ether-maleic acid anhydride copolymer, ethylene-maleic acid anhydride copolymer, vinyl butyl ether-maleic acid anhydride copolymer, acrylonitrile-methyl acrylate-maleic acid anhydride copolymer, butyl acrylate-styrene-maleic acid anhydride copolymer, polyvinyl alcohol phthalate, polyvinyl acetal phthalate, polyvinyl butylate phthalate and polyvinyl acetoacetal phthalate.

8. The pharmaceutical preparation of Claim 1, 2, 3, 4, 5, 6 or 7 wherein an intermediate layer comprising at least one member selected from the group consisting of a medicament and a water-soluble substance is provided between said polymer film soluble at low pH and said enteric coating film.

FIG. 1

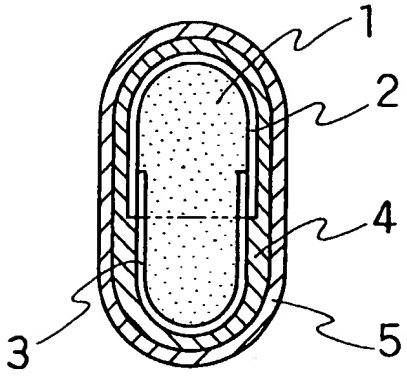

FIG. 2

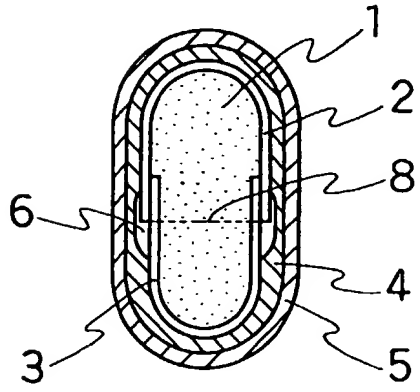

FIG. 3

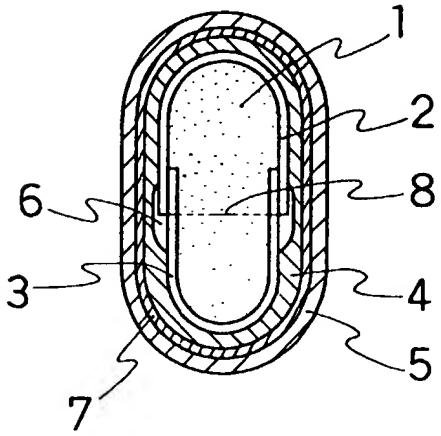

FIG. 4

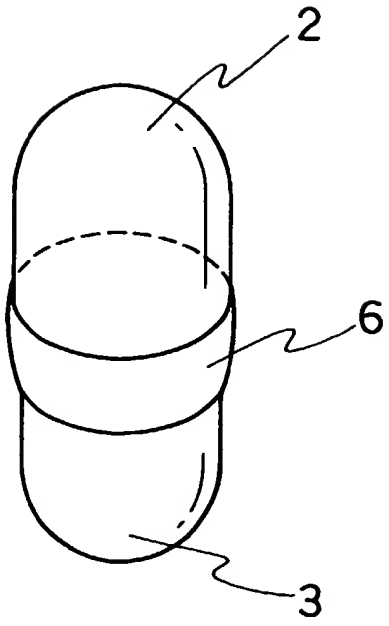

FIG. 5

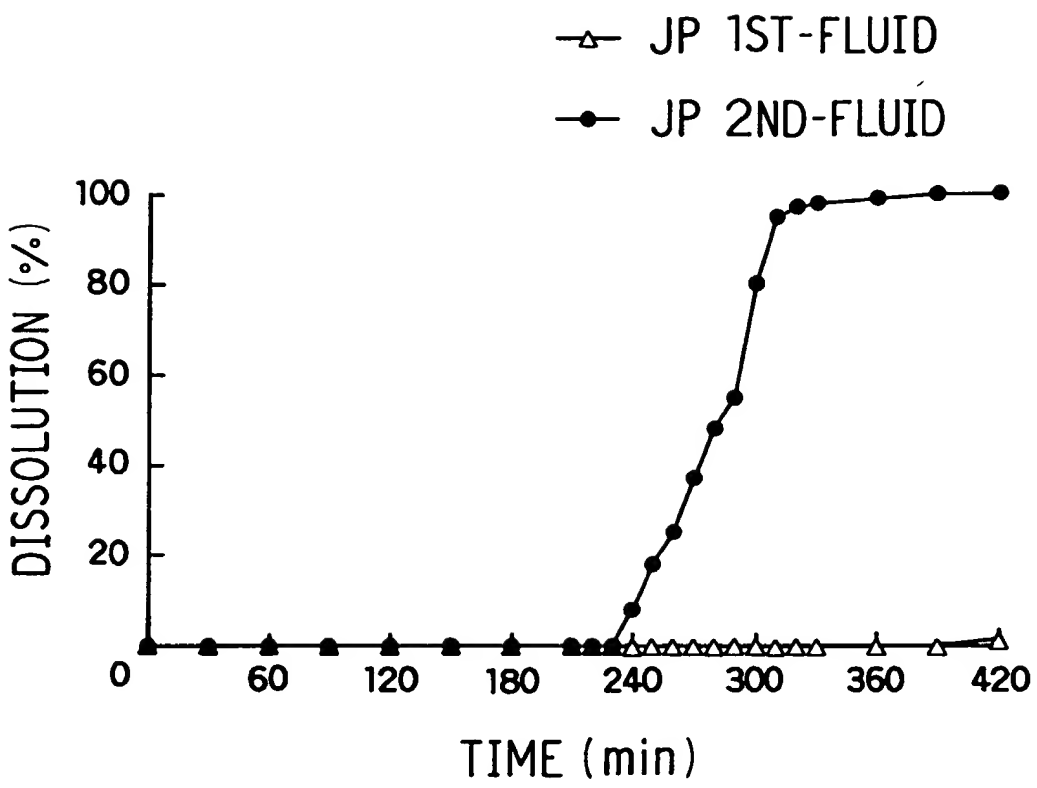
JP 1ST-FLUID
JP 2ND-FLUID
DISSOLUTION (%)
100
80
60
40
20
0
60
120
180
240
300
360
420
TIME (min)

FIG. 6

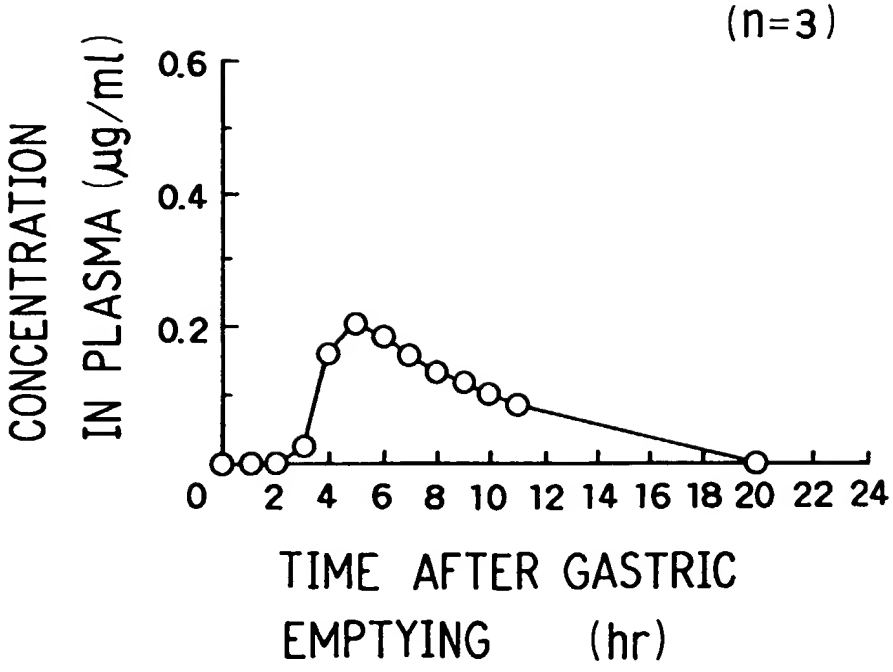
(n=3)
CONCENTRATION IN PLASMA (μg/ml)
0.6
0.4
0.2
0
2 4 6 8 10 12 14 16 18 20 22 24
TIME AFTER GASTRIC EMPTYING (hr)

FIG. 7

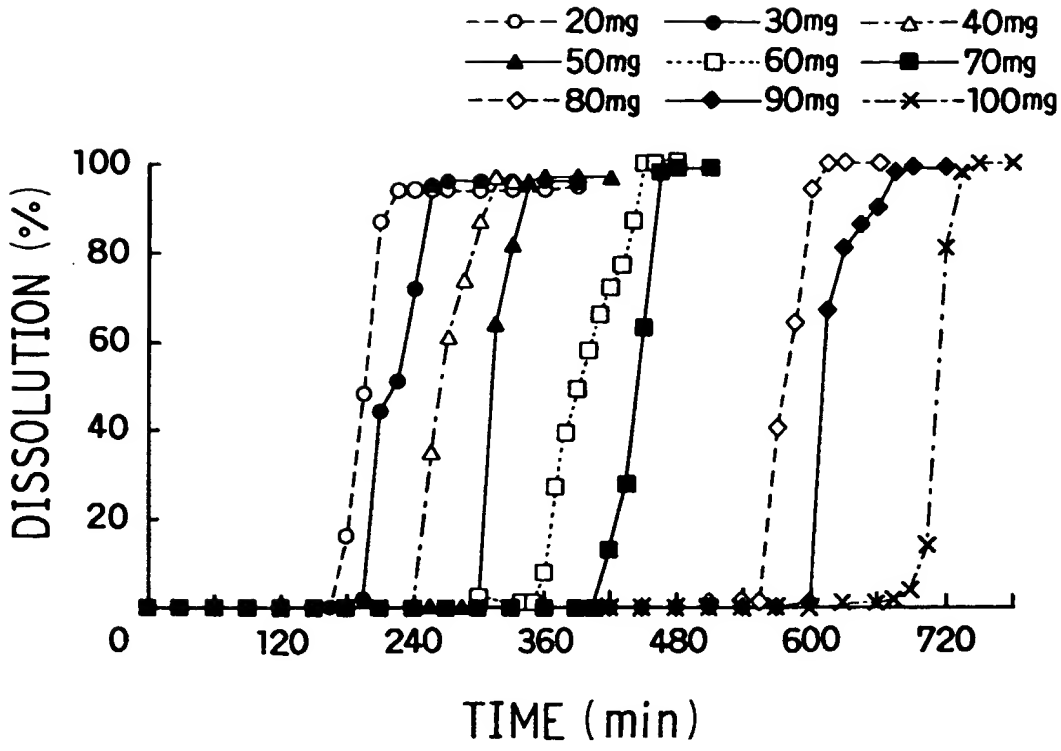
20mg
30mg
40mg
50mg
60mg
70mg
80mg
90mg
100mg
DISSOLUTION (%)
100
80
60
40
20
0
120
240
360
480
600
720
TIME (min)

FIG. 8

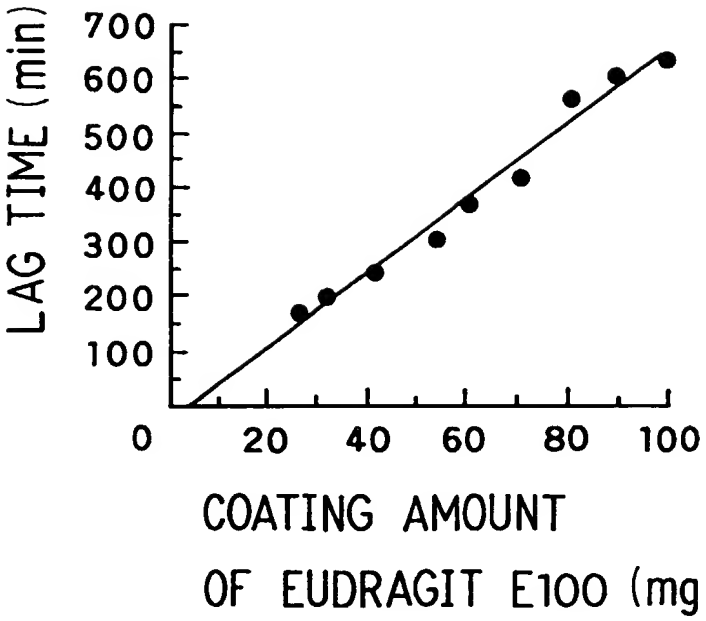
LAG TIME (min)
700
600
500
400
300
200
100
0
20
40
60
80
100
COATING AMOUNT
OF EUDRAGIT E100 (mg)

FIG. 9

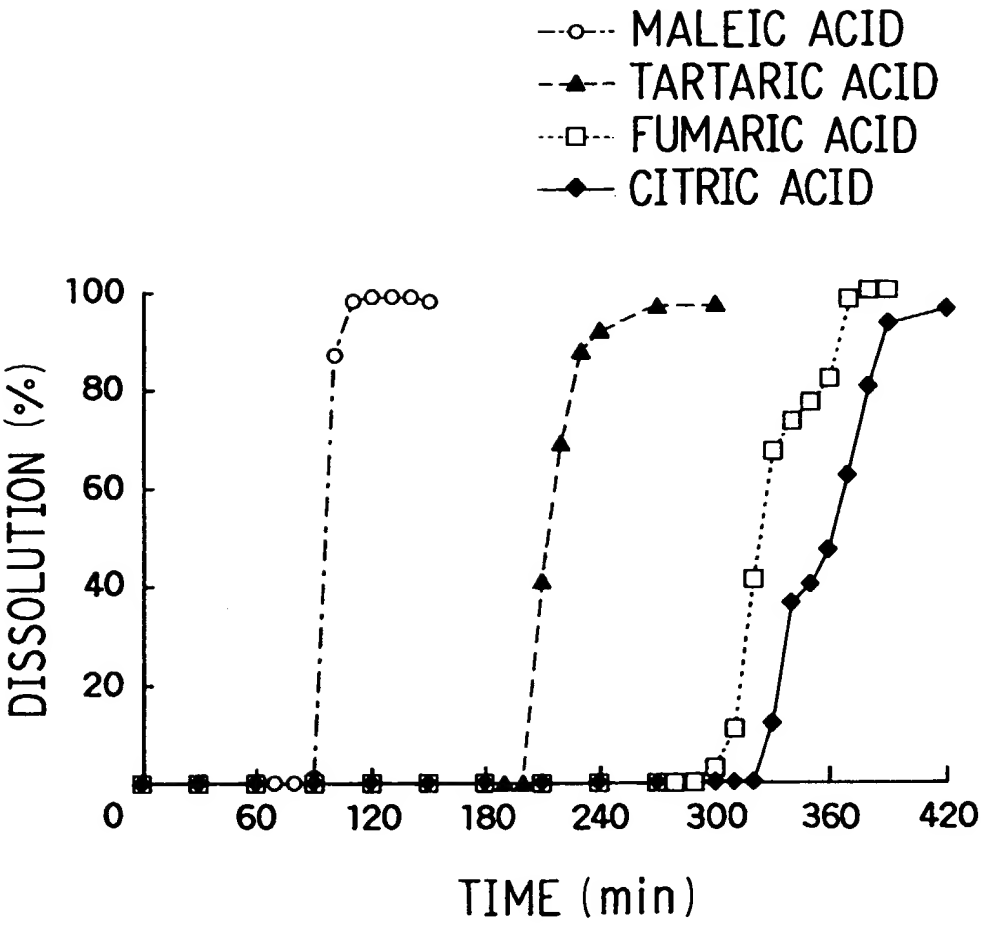
MALEIC ACID
TARTARIC ACID
FUMARIC ACID
CITRIC ACID
DISSOLUTION (%)
100
80
60
40
20
0
60
120
180
240
300
360
420
TIME (min)

FIG. 10

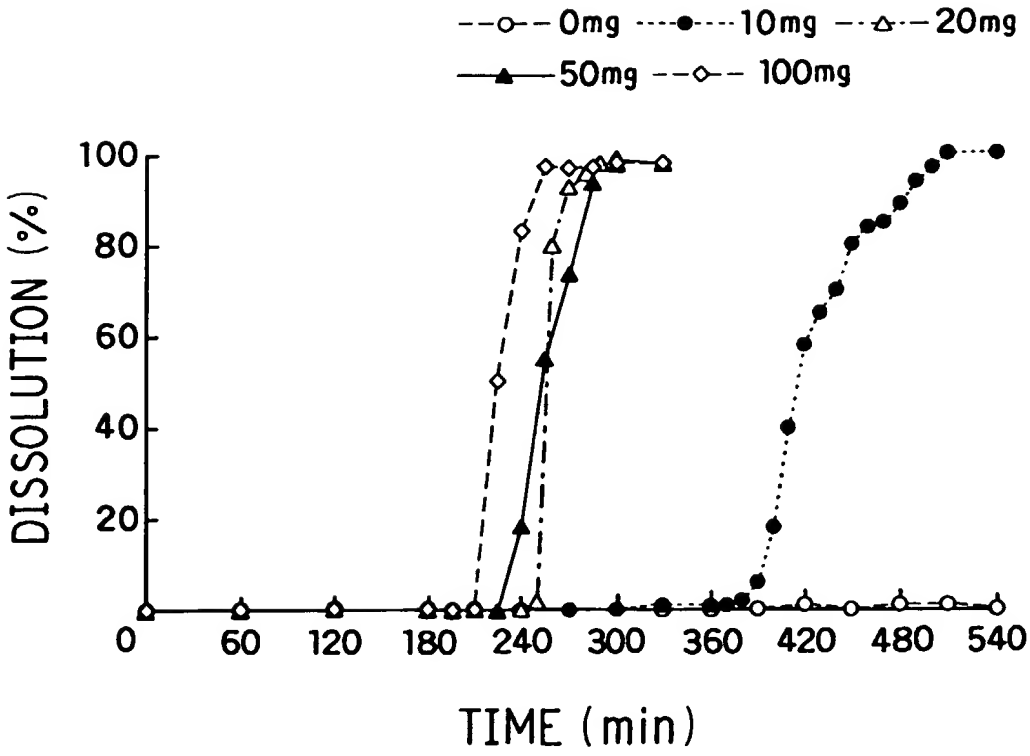
0mg
10mg
20mg
50mg
100mg
DISSOLUTION (%)
100
80
60
40
20
0
60
120
180
240
300
360
420
480
540
TIME (min)

FIG. 11